PULMONARY FAT EMBOLISM FOLLOWING INFUSIONS VIA THE BONE MARROW[1]

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Following the demonstration by Tocantins and his coworkers (1, 2) of the feasibility of introducing blood and other fluids into the body by way of the bone marrow, it was felt that this route might be applicable to the massive arsenotherapy of syphilis by the drip method (3). In human beings, Tocantins advises this route only when veins are not accessible, as in infants and obese adults. If massive arsenotherapy should be more widely used, and if it should be applied to children, an increasing number of patients with inaccessible veins would be encountered. An experiment was therefore planned to determine what effect mapharsen solution given by this route might have on the bone marrow and the other viscera.

METHOD

Nine adult male rabbits of various breeds, weighing from 2200 to 5600 gms. were used. The tibia, femur and humerus were the bones selected for injection. In preliminary experiments the 15 gauge needle used by Tocantins in human beings was found to be too large, causing later fractures at the site. Smaller needles, when used without a stilette, were too fragile and bent when introduction through bone was attempted. In a few rabbits the bone was exposed and trephined with an electric dental burr. This, however, was found unsatisfactory, as it was difficult to fit the needle exactly into the burr hole, and leakage from the bone resulted. A sharp 18 gauge needle with fitted stilette, similar to a lumbar puncture needle, was finally found to be most satisfactory, and was used throughout the experiment. The needle was inserted through the skin until bone was reached, and then rotated with moderate pressure until the tip entered the marrow cavity. Aspiration of blood marrow mixture was only occasionally successful, due probably to the small calibre of the needle. After injection by syringe of 2 to 3 cc. of fluid to clear the lumen and to make certain that the tip was securely in the marrow cavity, the gravity drip apparatus was attached. This consisted of a 50 cc. graduated glass burette, with a drip bulb, to which was attached by a Y tube an inverted flask of the solution, in order to refill the burette during the infusion. In some animals the same bone was utilized for two or even three daily treatments, but in most cases a different bone was used each day.

Light anesthesia was maintained during the entire course of each treatment by repeated intraperitoneal injections of sodium pentobarbital. At the time of introduction of the needle into the bone, this was reinforced by brief ether

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inhalation. No mechanical restraint was used, the rabbit lying drowsily on its side during the entire course of the infusion. The total amount of sodium pentobarbital used in the five days of treatment ranged from 412 to 1600 mgms.

The daily dose of mapharsen[2] was 4 mgm. per kilo. body weight, in a dilution of 1 mgm. mapharsen in 10 cc. of 5% dextrose solution. Seven rabbits were given five successive daily bone marrow infusions, and were sacrificed from the 5th to the 19th day of the experiment. Two control animals, which received five daily intravenous infusions, the dosage and dilution of the drug and the experimental conditions, including anesthesia, being identical to those used in the test group, were killed on the 10th and 16th days. All animals were sacrificed by rapid injection of about 5 cc. of air into the marginal ear vein, except for rabbits ⁂48 and ⁂28, which died on the 5th and 7th days respectively. Histologic study of the bones and viscera was made in each case.[3] The mean speed of injection for each animal for the five days of treatment ranged from 1.3 to 6.3

TABLE 1

Massive arsenotherapy by bone marrow infusion

Five daily treatments of four milligrams mapharsen per kilogram body weight, in a dilution of one milligram mapharsen to ten cc. of five per cent glucose

RABBIT NO.	INITIAL WEIGHT	TOTAL VOLUME INJECTED INTO BONE MARROW IN 5 DAYS	SPEED OF INFUSION, CC./MIN.			PULMONARY FAT EMBOLISM
			Highest	Lowest	Mean for 5 days	
	gms.	*cc.*				
48	2405	478	10.9	4.1	6.3	+
46	2410	457	9.3	1.4	5.1	
29	4070	813	4.8	0.8	3.3	+
23	4200	807	5.1	1.3	3.0	+
28	5585	1117	4.1	1.1	2.9	+
45	2245	431	5.4	1.4	2.7	
44	2510	466	2.7	1.3	2.3	+

cc. per minute, and the total duration of treatment for the five days from 89 to 349 minutes.

RESULTS

Rabbit ⁂48 died suddenly at the end of the fifth treatment in a manner suggesting pulmonary embolism. No air bubbles were seen in the infusion apparatus. Rabbit ⁂28 died two days after the end of treatment. The remaining animals appeared healthy throughout, although most of them lost weight.

The most striking pathological finding was fat embolism in the pulmonary arterioles, which was seen in 5 of the 7 rabbits treated by the bone marrow route (see table 1). In one of these (⁂48), fat embolism was the cause of sudden death

[2] We are indebted to Parke Davis and Co. for the mapharsen used in this study.

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FIG. 1. HEMATOXYLIN-EOSIN STAIN OF LUNG (RABBIT #48)
Pulmonary arterioles containing large globules. Note foreign body giant cells (× 430)

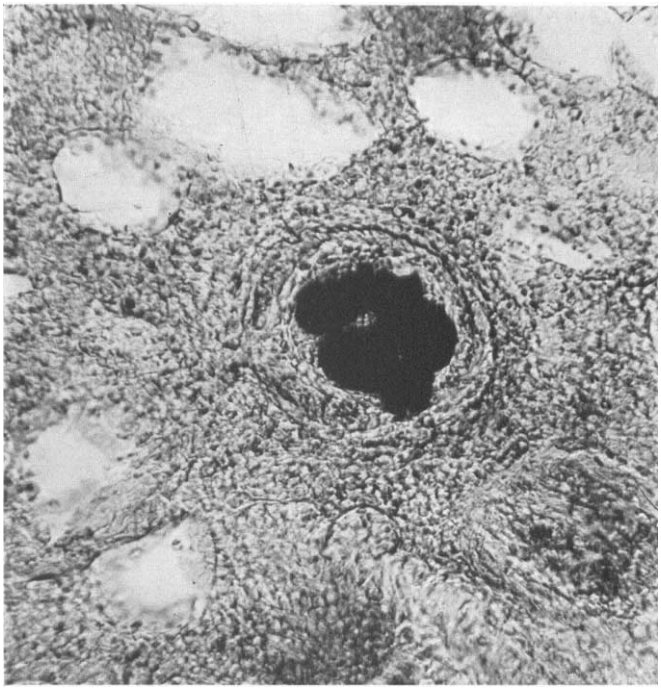

FIG. 2. OSMIC ACID STAIN OF LUNG (RABBIT #29)
Pulmonary arteriole containing fat globules (× 430)

at the termination of the fifth treatment. In the others, there was no immediate or delayed clinical evidence of emboli. Hematoxylin-eosin stains showed unstained large globules, in most cases surrounded by foreign body giant cells, filling the pulmonary arterioles (fig. 1). That these were fat globules was demonstrated by Scharlach R and osmic acid stains in two of the animals (fig. 2). In pathologic sections, one control rabbit which received intravenous treatment showed evidence of multiple pulmonary emboli, which probably were caused by air through faulty intravenous technic; no fat globules were seen. Lung sections in the other control rabbit were negative.

Many of the injected bone marrows showed some localized hemorrhage, fragmentation of bone, necrosis and polymorphonuclear infiltration, but normal hematopoesis was seen in each animal. Petechial hemorrhages were seen occasionally in the lung, spleen, heart, muscle, brain, and in bone marrow not the site of injection. Acute passive congestion was seen frequently in the liver and lung, less often in kidney, spleen, heart, and brain. Toxic hepatitis, with focal necrosis, was observed in one rabbit, bile duct proliferation, probably the healed stage of a toxic hepatitis in another, and fatty infiltration in several. Cloudy swelling, desquamation of tubular epithelium, and acute toxic nephritis of varying degrees were seen in the kidney. The heart showed cellular infiltration, vacuolar degeneration, and cloudy swelling in several instances. In one rabbit, perivascular lymphocytic and mononuclear phagocyte infiltration was seen in the brain. Except for occasional edema, the spleen was not unusual. With the exception of pulmonary fat embolism and traumatic bone changes, no essential difference was noted in the histologic studies between rabbits treated by bone marrow and those treated by intravenous infusion.

DISCUSSION

Tocantins (1) states "there seems to be little ground for fearing fat embolism" as a result of bone marrow infusions, although he concedes that "some fat is conceivably displaced into the blood stream". No evidence of fat embolism was noted in the 40 patients he treated. However, many non-fatal cases are not recognized because of the lack of a clear-cut clinical picture (4).

It would seem probable that the more rapid the bone marrow infusion and the higher the pressure of the stream of fluid, the greater would be the likelihood of rupturing fat cells and forcing fat globules into the venous system. It is of interest to note that the only fatal fat embolism in this study occurred at the termination of the most rapid infusion of the entire series, at a rate of 10.9 cc. per minute. It may be seen in table 1, however, that speed of injection was not the sole determining factor in the occurrence of fat embolism. Tocantins (1) reports infusion speeds in human beings of 0.4 to 25 cc. per minute, and in one case syringe injection at 43 cc. per minute. It would appear, on the basis of this study, that bone marrow infusion may carry fat globules from the bone marrow into the blood stream, whence they are deposited as emboli in the lung capillaries. further experimental work should be carried out before bone marrow infusion can be accepted as a safe procedure in human beings.

Except for fat embolism, the visceral histologic damage seen in rabbits treated by bone marrow infusion was essentially the same as that seen in rabbits treated by vein. The toxicity of mapharsen does not appear to be altered by the former route. Gruhzit (5) and Magnuson and Raulston (6) found similar changes in animals following large doses of mapharsen given intravenously.

SUMMARY

Seven rabbits were given massive arsenotherapy by bone marrow infusion drip, 4 mgm. of mapharsen per kilo. body weight, each day for five successive days. In two control rabbits, intravenous massive arsenotherapy was administered.

Pulmonary fat emboli were demonstrated in 5 of the 7 rabbits treated via the bone marrow. No fat emboli were seen in the two animals treated by vein.

CONCLUSION

In view of the finding of pulmonary fat embolism in animals treated by bone marrow infusion, this procedure cannot at present be considered free from hazard in human beings.

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